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Benign prostatic hyperplasia- treatment and monitoring

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Introduction

The treatment of benign prostatic hyperplasia (BPH) depends on how pronounced the lower urinary tract symptoms (LUTS) are and if they are effecting the quality of life of the patient. Treatment interventions include surgery, pharmacological treatment and lifestyle measures – all of which can have an overall positive effect. In addition to this, it is appropriate to consider “watchful waiting” where patients are closely monitored to ensure that their condition is stable and an intervention is made at an appropriate point, should it be required. This approach has been shown to be safe and acceptable to patients.¹

Lifestyle Changes

For patients who have less troublesome (IPSS<7) symptoms there is an option to employ “watchful waiting” in combination with practical advice, which may help to reduce the impact of LUTS. Clearly, careful thought around the consumption of fluids with regard to volume and timing may minimise the impact of nocturia. In addition, avoidance of caffeinated beverages and spicy foods may be of some benefit.

Pharmacists should be aware of concomitant medication and the potential for it to adversely affect the patient’s LUTS; for example, the use and timing of diuretics is an important consideration. Other drugs such as decongestants, antihistamines and antidepressants may also complicate symptoms.

Use of pads or containment products may also be helpful, but in terms of patient acceptability they may be less desirable. Such measures are less likely to be effective for patients who have a significant degree of outlet obstruction.

Pharmacological Treatment

The aim of pharmacological intervention is to reduce bladder and prostate smooth muscle tone or to alter the size of the prostate and thus reduce resistance to flow of urine.

Alpha-adrenoceptor antagonists

The bladder neck and prostate contains numerous α_1 - and α_2 -adrenoceptors within the smooth muscle tissue, with preponderance of the α_1 subtype. Drugs which act as antagonists at these receptors have been shown to improve urinary flow. Older drugs which antagonised both α_1 and α_2 -adrenoceptors caused significant side effects due to the antagonism of α_2 receptors within the cardiovascular system. Newer drugs have a higher relative affinity for α_1 receptors and are therefore associated with less cardiovascular side effects. The drugs currently prescribed for BPH include tamsulosin, terazosin, alfuzosin and doxazosin. Most are available as convenient once daily, controlled-release preparations. In general, there appears to be little difference in terms of overall

efficacy with a 2-3mL/s increase in maximum urinary flow rate and improvement in other LUTS symptoms and subsequent IPSS score.² As the action of alpha-adrenoceptor antagonists is restricted to alteration in muscle tone there is no decrease in prostate size or subsequent rate of growth. In addition, there is no fall in PSA and it has been observed that patients prescribed alpha-adrenoceptor antagonists show no reduction in terms of the necessity to have surgery at some point in the disease progression.³ NICE guidance for the management of lower urinary tract symptoms in men⁴ recommends that alpha-adrenoceptor antagonists be prescribed with moderate to severe LUTS and that patients should be reviewed after 4-6 weeks of starting therapy, and then annually thereafter. Around 15% of patients⁵ will experience mild side-effects including headache, dizziness, drowsiness and postural hypotension. Patients should be counselled in terms of the likelihood of first-dose hypotension and that the first dose is best taken where they retire to bed and should symptoms such as dizziness, fatigue or sweating occur that they remain lying down until they resolve.⁶ Some men may experience problems with retrograde ejaculation in association with these drugs. The decision around which specific agent to use should be made with regard to patient comorbidities and tolerance.

Tamsulosin is licensed for 'over the counter' sale within pharmacies for treatment of functional symptoms of BPH in males aged 45 to 75 years. It is available as a 400 microgram modified release capsule and can be taken for up to six weeks before the patient must be assessed by a G.P. Any patient whose symptoms have not improved, or have worsened within 14 days of starting treatment should be referred for assessment by their general practitioner. Community pharmacists should be fully aware of the complexity of management in this area particularly in the context of the differential between BPH and prostatic carcinoma. In addition, it is an excellent opportunity for men to discuss LUTS with a health professional where they may otherwise not consider going to see their GP. Many men see problems with their urinary tract as an inevitable consequence of getting older, and whilst that this may partially be true it can be managed in a constructive way which may have less impact on the patient's quality of life if appropriate medical intervention is sought.

5 α -reductase inhibitors (5ARIs)

The 5ARIs are indicated for men with LUTS, significantly enlarged prostate glands or those with a high PSA >1.4ng/mL and a high likelihood of progression of the condition.⁴

Testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5 α -reductase in the normal process of androgen metabolism. This exists as two isoenzymes, 5 α -reductase I and II with isoenzyme II being the most plentiful within the prostate. DHT is significantly more potent than testosterone and is one of the driving factors in normal and abnormal prostatic growth. The 5ARIs inhibit this conversion and thus have a beneficial effect upon BPH and LUTS.

There are two 5ARIs licensed for the treatment of BPH; finasteride and dutasteride. Finasteride is a Type II 5 α -reductase inhibitor and, as such, is less effective at reducing the overall serum concentration of DHT when compared to dutasteride, which inhibits both Types I and II. Both drugs significantly reduce serum DHT levels; reductions in prostate volume of 20-30% have been observed as has an improvement on the IPSS scale (typically 3-4.5 points) and an increase in maximum urinary flow (typically 1.5-2.5 mL/s) of.⁷ These effects are generally seen within 3-6 months of commencing treatment and persist for a significant duration. Both drugs also reduce the risk of the development of acute urinary retention (AUR) and the need for surgery in comparison to placebo.^{8,9}

In addition, both 5ARIs cause reductions in PSA; as such it is likely that the PSA reference range, in the context of prostate cancer detection, be reconsidered for patients taking 5ARIs.

The side effect profile of these drugs is primarily concerned with sexual function, which is predicted from the mechanism of action, with patients experiencing loss of libido, erectile and ejaculatory dysfunction. Some men may also experience breast tenderness. It should be noted that both drugs are present in semen and this could be an issue if the patient's partner is pregnant or likely to become pregnant. In such cases patients should be advised to use a condom to prevent the potential for the woman to absorb the drug. Women should also be advised to avoid handling broken tablets of finasteride or leaking capsules of dutasteride for the same reasons.

Initially, patients taking 5ARIs should be reviewed at 3-6 months and thereafter every 6-12 months.

Combination Treatment

In view of the mechanism of action of the alpha-adrenoceptor antagonists and the 5ARIs, the use of both classes of drug in combination is logical from a pharmacological point of view. Indeed, when these agents are used in combination, the immediate relief of symptoms offered by the alpha-adrenoceptor antagonists and the long-term benefits in terms of reduction in prostate size and risk of both AUR and surgical intervention shown by the 5ARIs are beneficial. The combination of doxazosin and finasteride was shown to be significantly superior to either doxazosin or finasteride alone in the context of clinical progression of BPH, symptom score, maximum urinary flow rates or development of AUR and or the need for BPH related surgery.¹⁰ The combination of dutasteride and tamsulosin has also recently been investigated¹¹. Results are similar with overall improvement seen with regard to symptoms, symptom score, reduced disease progression and a lower incidence of AUR and the need for surgical intervention. Combination therapy is of clear benefit for men with moderate to severe LUTS and large prostates estimated at over 30g.

Monitoring in combination therapy should be as above, which was discussed for the individual agents. Patients who respond to combination therapy may discontinue the alpha-adrenoceptor antagonist after 6-9 months. The patient may then continue with monotherapy or if symptoms recur they should restart the combination therapy.

Antimuscarinic Drugs

Patients who present with BPH with a significant component of detrusor over activity may benefit from a combination of alpha-adrenoceptor antagonist and an antimuscarinic drug, such as oxybutynin. Clearly, this could become complex for patients who have a history of AUR and should be approached with care in such cases. Elderly patients with a history of cardiovascular disease or angle-closure glaucoma are also a risk when considering this combination of drugs.

Herbal Treatments

There are a number of herbal treatments available for the treatment of LUTS associated with BPH. Most contain the herbal extract *Serenoa repens* (Saw Palmetto). There is limited trial evidence in the literature to support such products and what does exist is conflicting in nature. Certainly the largest clinical trial to date that examined the use of Saw Palmetto did not give any convincing results, with all measurable aspects of BPH not improved when compared to placebo.¹² At this time, due to the

lack of good quality clinical evidence, it is difficult for health professionals to recommend such treatments for BPH.

Surgical Intervention

Many patients will ultimately require surgical intervention to control complications of LUTS. In the case of AUR patients present with painful retention of urine which needs to be relived immediately. It is resolved, in the short-term, with the introduction of a urinary catheter. Patients may also present with chronic retention where a painless but palpable bladder can develop over an extended period of time giving rise to the potential for renal failure, hypertension and chronic infection. Once catheterised, these patients may then suffer a significant loss of urine which could lead to electrolyte imbalance. In cases of both acute and chronic retention, patients are often referred for prostatectomy – clearly this is associated with risks and the potential to affect urinary continence and sexual function following the surgery. In the case of acute retention, emergency surgery may be required, which has significantly higher risks than elective surgery for chronic retention.⁵

In some cases of AUR men may be selected for trial without catheter. In such cases, patients may be given alpha-adrenoceptor antagonists to improve the likelihood of voiding without surgical intervention.^{13, 14}

Other patients will require surgery due to the fact that medical treatment has failed or the patient has chosen to have the problem surgically corrected. The aim of surgical intervention is to remove the obstruction to the flow of urine or to solve complication associated with LUTS such as AUR, gross haematuria, renal failure or bladder calculi associated with BPH or BPH related obstruction. There are a number of surgical options:

Transurethral resection of the prostate (TURP)

This is the “gold standard” procedure and has improved dramatically in recent years in terms of the need to repeat the procedure as well as associated morbidity and mortality. The TURP involves using a diathermy current through a fine metal loop which effectively cuts away the offending tissue. The developments in the equipment used to perform the procedure have significantly enhanced the safety profile. There is a significant risk of blood loss during surgery and that may require a transfusion to correct the deficit. Patients can also suffer from TURP syndrome where an extended surgical period has resulted in patients absorbing excessive amounts of irrigation fluid and thus developing hyponatraemia. Some men may experience impotence and incontinence but the risks are low, while others may develop retrograde ejaculation.¹⁵

Transurethral incision of the prostate (TUIP)

This procedure is primarily considered for men who are sexually active and wish to retain outward ejaculation. TURP has a significant rate of retrograde ejaculation with around 90% of men being affected, while , in contrast, only 15-30% will be affected after TUIP.¹⁵ This procedure involves a different type of incision and thus reduces the risk of ejaculatory dysfunction.

Laser prostatectomy

Various laser sources have proved useful in prostatic surgery. Holmium laser enucleation (HoLEP) has been compared to TURP and has shown positive outcomes in terms of immediate post-surgical and longer terms benefits.¹⁶ The benefit of this approach is clear in patients with larger prostates and also those who may be at increased bleeding risk, such as patients taking long-term anticoagulants or those who have bled profusely on catheterisation.

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